

REMARKS

This Amendment responds to the Office Action mailed on September 16, 2008. In the Office Action, the Examiner:

- requested a specific reference to the prior-filed applications in compliance with 37 CFR 1.78(a) to be included in the first sentence(s) of the specification;
- requested Applicant to provide a copy of each non-patent literature publication in compliance with 37 CFR 1.98(a)(2);
- rejected claims 49 and 57-64 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement;
- rejected claims 49 and 61-62 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Wolff, M.E. Burger's Medicinal Chemistry 4th Ed. Part I, Wiley: New York, 1979,336-337;
- rejected claims 57-60 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Bilodeau *et al.* U.S. Patent Publication No. 2002/0137755; and
- rejected claims 63-64 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Kovesdi *et al.* U.S. Patent Publication No. 2003/45498.

Claims 49 and 57-64 are pending. A specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) is added in the first sentence of the specification. No new matter is added by this Amendment.

I. Priority

On page 2 of the Office Action, the Examiner stated that if Applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. CIP of 10/699,154, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title. Further, for benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

The declaration filed with this application on January 22, 2007 clearly claims priority to both PCT Application No. PCT/US2004/13252 and U.S. Application No. 10/699,154. In

compliance with 37 CFR 1.78(a), the specification has been amended to add a first sentence to claim priority to both applications.

Further, the first sentence of U.S. Application No. 10/699,154 claims priority to U.S. Provisional Application No. 60/422,899, filed October 31, 2002. Therefore, the first sentence of this application also claims priority to U.S. Provisional Application No. 60/422,899.

Because the specification of this application on page 39, lines 15-16 states that all cited references are incorporated by reference and the declaration, which was filed together with this application at the same time, cites PCT Application No. PCT/US2004/13252 and U.S. Application No. 10/699,154, the first sentence of this specification also incorporates the PCT and U.S. non-provisional and provisional applications by reference. Therefore, there is no new matter and entry of this amendment is requested.

II. Information Disclosure Statement

On page 4 of the Office Action, the Examiner alleged that Applicant had failed to provide a copy of each non-patent references listed in the Information Disclosure Statement (IDS) in compliance with 37 CFR 1.98(a)(2).

The IDS lists references A01-A55, B01-B08 and C01-C07 where C01-C07 are non-patent references. This application claims priority under 35 U.S.C. § 120 of U.S. Patent Application No. 10/669,154 filed on October 30, 2003 and therefore the copies of non-patent references C01-C07 were not submitted pursuant to 37 C.F.R. § 1.98(d). Further, these C01-C07 references were submitted on 7/27/2004, 11/12/2004, 03/01/2005 and 11/02/2005 for U.S. Patent Application No. 10/669,154 and they currently appear as NPL documents dated 7/27/2004, 11/12/2004, 03/01/2005 and 11/02/2005 in the electronic file wrapper of the 10/669,154 application. Therefore, they are ready available to the Examiner. However, Applicant will re-submit the C01-C07 references upon further request by the Examiner.

III. The Rejection of Claims 49 and 57-64 under 35 U.S.C. § 112 Should Be Withdrawn

On page 4 of the Office Action, the Examiner rejected claims 49 and 57-64 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleged that Applicant does not demonstrate the preparation of the specific

compound 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline at the time of the invention for the treatment as claimed. Applicant respectfully disagrees.

Applicant respectfully submits that the rejection is improper and should be withdrawn for the following reason. The specification of this application cites U.S. Patent No. 6,403,613 on page 8, line 28 and on page 39, lines 15-16 states that all cited references are incorporated by reference in their entirety. U.S. Patent No. 6,403,613 on col. 9, line 50 to col. 10, line 5 discloses the preparation of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline. Therefore, claims 49 and 57-64 contain subject matter which was clearly described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

In view of the disclosure of the application, Applicant respectfully requests withdrawal of the rejection of claims 49 and 57-64 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

IV. The Rejection of Claims 49 and 61-62 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 6 of the Office Action, the Examiner rejected claims 49 and 61-62 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Wolff, M.E. Burger's Medicinal Chemistry 4th Ed. Part I, Wiley: New York, 1979,336-337. Applicant respectfully disagrees.

Claim 49 is drawn to a method of treating macular degeneration, which comprises administering to patient having macular degeneration a pharmaceutically effective amount of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-methylisoindoline or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

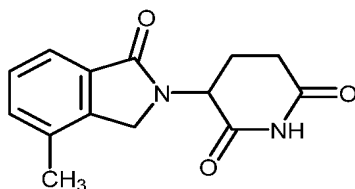
The Examiner alleged that (1) D'Amato teaches a compound (*i.e.*, the middle compound in the top row of Figure 1) without a methyl group with the exact same core structure as claimed in the instant claims where all the variables are H, alkyl analogs of the instant claims, are prima facie obvious and require no secondary teaching; (2) D'Amato in Column 7 teaches formula A with various substitution including methyl group; and (3) Wolff in Table 8.2 teaches that the addition of alkyl groups to active pharmacological agents often improves activity and bioavailability by increasing lipophilicity.

The current standard of obviousness takes into account (1) whether there would have been a “reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;” and (2) whether the combination of elements would have yielded “predictable results” *i.e.*, whether there would have been a reasonable expectation of success. (*See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) (“The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.”) (emphasis added, internal quotations omitted)).

With regard to the instant case, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicant respectfully submits the following:

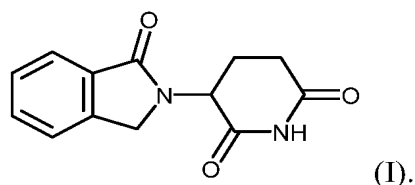
- (1) The cited references would not have provided any reason to select the claimed compound for the treatment of macular degeneration; and
 - (2) The cited references would not have provided the legally required reasonable expectation of success.
1. The cited references would not have provided any reason to select the claimed compound for the treatment of macular degeneration.

The Examiner’s rejection is flawed because it relies on the false assumption that D’Amato actually discloses 1-oxo-2-(2,6-dioxopiperidin-3-yl)-methylisoindoline (“the instant compound”):

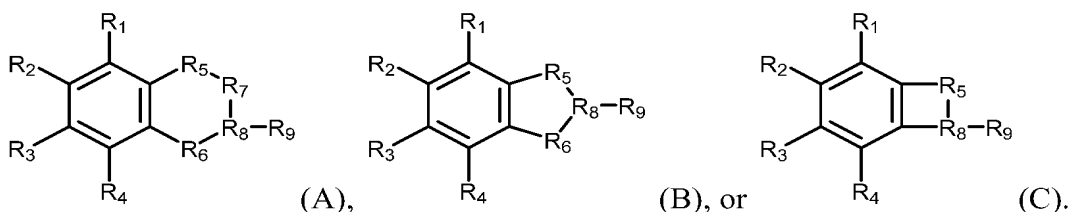


Indeed, the Examiner has admitted that the instant compound is not disclosed as an individual species in D’Amato. See the first sentence of the third paragraph on page 6 of the Office Action.

Further, the Examiner relies on the false assumption that D'Amato teaches methyl substitution to the core structure (I) as shown below:



As indicated by the Examiner, D'Amato merely teaches methyl substitution to formula A, B or C as shown below but not to the core structure (I) because the core structure (I) cannot be derived from any of formula A, B or C.



To derive the core structure (I) from any of formula A, B or C, R₈ has to be a **nitrogen atom** but not any of the nitrogen-containing groups as defined for R₈ in col. 7 of D'Amato. Because D'Amato and Wolff, individually or in combination, do not teach, suggest or modify R₈ to be a nitrogen atom, it would not have been obvious to one of ordinary skill in the art at the time the claimed invention was made to methylate the core structure (I) at the 4-position to produce the instant compound.

The examiner further argues that the core structure (I) is disclosed in Figure 1 of D'Amato and the substitution of a hydrogen of the core structure (I) with a methyl is *prima facie* obvious. Applicant respectfully disagrees because D'Amato does not teach the methylation of the core structure (I), much less at the 4-position of the core structure (I) for the reasons discussed above.

Further, as the Federal Circuit recently made clear in *Takeda* and even more recently in *Eisai*, allegations of structural similarity alone are insufficient to support the obviousness of a chemical modification, such as methylation. *Eisai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Takeda Chemical Industries, Ltd. v. Alphapharm*

Pty., Ltd. 492 F.3d 1350, 1361 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 1739 (2008).

Instead, “it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.”) (emphasis added). *Takeda*, 492 F.3d at 1357.¹

For example, in *Takeda*, the Federal Circuit considered the obviousness of performing a modification that involved “homologation” by one carbon and a change in aromatic ring position, *i.e.* ring walking. 492 F.3d at 1353-54. Both structures under consideration had a common “core structure.” *Id.* However, the Court held that the modification was not obvious in part because “nothing in the [prior art] suggest[ed] to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success [and because] there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes.” *Id.* at 1361; *see also* Figure 1 below.

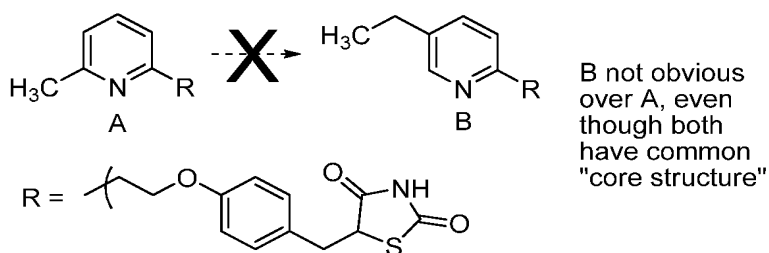


Figure 1. Compounds under consideration in *Takeda*.

In *Eisai*, the Federal Circuit considered the obviousness of replacing a 2, 2, 2-trifluoroethoxy substituent with a methoxypropoxy substituent. 533 F.3d at 1357. Both structures under consideration had a common “core structure.” *Id.* The Federal Circuit affirmed nonobviousness as a matter of law in part because “the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution.” *Id.* at 1359; *see also* Figure 2 below.

¹ Both *Takeda* and *Eisai* were decided after the landmark case of *KSR International Co. v. Teleflex*, which warned against the use of rigid and mandatory formulas in an obviousness determination. 127 S.Ct 1727, 1741 (2007) (“[W]hen a court transforms [a] general principle into a rigid rule that limits the obviousness inquiry...it errs.”); *see also* MPEP 2144.07 (“Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103.”). The Examiner’s reliance on structural similarity alone amounts to the same kind of inflexible “rigid and mandatory” formula that the Court in *KSR* warned is not proper for determinations of obviousness.

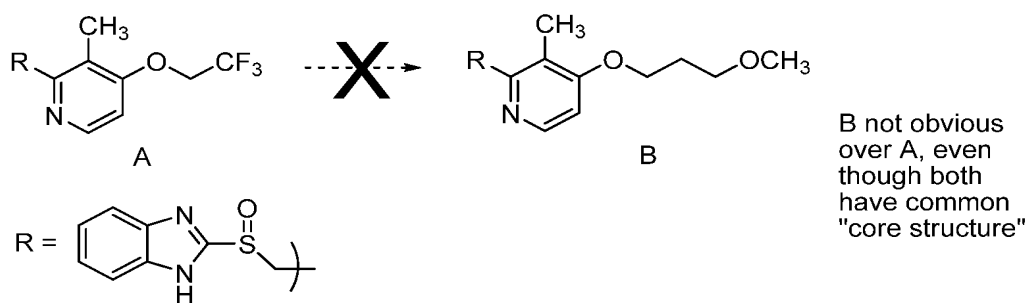
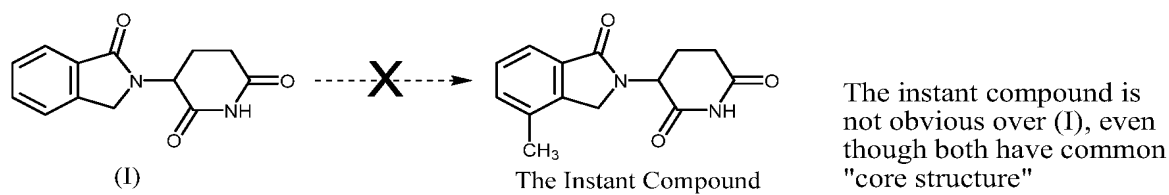


Figure 2. Compounds under consideration in *Eisai*.

Eisai and *Takeda* establish that both a reasoned approach to the needed modification and a reasonable expectation of success that the particular modification would work are necessary to establish a *prima facie* case of obviousness. In other words, the mere existence of a common core structure is not enough to render a modification obvious. *Eisai*, 533 F.3d at 1359; *Takeda*, 492 F.3d at 1361; *Sanofi III*, 492 F.Supp.2d at 392.

Thus, the PTO's reliance on a common core structure is wholly inconsistent with the current standard of obviousness under *Eisai*, *Takeda* and *Sanofi*. Instead, the Examiner must – but does not – establish that there would have been a reason for modifying core structure (I) to the instant compound as shown below for the methods within the instant claims.



Further, one ordinary skilled in the art would not be motivated to combine D'Amato with Wolff to arrive at the instant methods. Wolff merely teaches that the addition of alkyl groups to change lipophilicity and the duration of anesthesia. Thus, Wolff has nothing to do with treating macular degeneration as recited in the instant claims. Therefore, the Examiner has failed to establish that there would have been a reason for a skilled artisan to modify the teachings of cited references within the instant claims.

2. The cited references would not have provided the legally required reasonable expectation of success.

The Examiner has failed to explain how one skilled in the art would have had a reasonable expectation that the claimed compound would be effective in treating macular

degeneration. The Federal Circuit, following *KSR*, articulated guidelines for determining “whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious.” (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

[A]n invention would not be invalid for obviousness if the inventor would have been motivated to **vary all parameters or try each of numerous possible choices** until one possibly arrived at a successful result, where the prior art gave either **no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful**. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.* (citing *In re O’Farrell*, 953 F.2d 894, 903 (Fed. Cir. 1988))(internal quotations omitted) (emphasis added)).

In the instant case, to arrive at the instant methods, not only would one skilled in the art have had to “try each of numerous possible choices” of variables from the genus of D’Amato, but one skilled in the art would have also have had to “try each of numerous possible choices” in Table 8.2 of Wolff. Further, Wolff merely teaches that the addition of alkyl groups to change lipophilicity and the duration of anesthesia. Wolff is silent at to macular degeneration. Therefore, none of the cited references would have provided any “indication of which parameters were critical” or any “direction as to which of [the] many possible choices is likely to be successful.” As is evident from *PharmaStem*, this scenario is exactly what the Federal Circuit warned is **not** a legally sufficient “reasonable expectation of success.” (*Id.*). The combination of references, at most, would have merely provided general guidance and would have merely provided a list of many disorders and a list of many compounds – none of which is actually the instant compound – without any indication as to why the instant compound would be specifically useful for the recited macular degeneration. Thus, the cited references do not provide the requisite expectation of success, and the rejection should be withdrawn.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 49 and 61-62 under 35 U.S.C. § 103(a) as being unpatentable over D’Amato (U.S. Patent No. 6,469,045) in view of Wolff.

V. The Rejection of Claims 57-60 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 8 of the Office Action, the Examiner rejected claims 57-60 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato as applied to claims 49, 61 and 62 above (U.S. Patent No. 6,469,045) in view of Bilodeau *et al.* (U.S. Patent Publication No. 2002/0137755). Applicant respectfully disagrees.

The Examiner alleged that (1) D'Amato teaches the treatment of ocular neovascular diseases associated with angiogenesis (Column 1 line 65-66) including macular degeneration (column 2 line 3-6) with antiangiogenesis compounds like thalidomide derivatives; (2) Bildeau *et al.* teaches the use of therapeutically effective amount of several second compounds like antiangiogenesis agents (Page 63 claims 35 and 36) for diseases related to angiogenesis including macular degeneration; (3) Bildeau *et al.* teaching includes modulators of hormone receptor, retinoid receptor, cytotoxic and antiproliferative agents and enzyme inhibitor which could encompass compounds claimed as a second agent in claim 58 (Page 63 claim 22, 29 and 30); and (4) Bildeau *et al.* teaches the thalidomide as a second agent as claimed in claim 59 and 60 (Page 15 [0259], page 63 claim 30).

Claims 57-60 depend on claim 49. As explained in section (IV) above, D'Amato does not teach or suggest the method of claim 49. Bildeau *et al.* also does not teach or suggest the instant compound, much less the method of treating macular degeneration with the instant compound. Therefore, D'Amato and Bildeau *et al.*, individually or in combination, do not teach or suggest the use of the method of claim 49 and thus claims 57-60 for treating macular degeneration.

In view of the above comments, Applicant respectfully requests withdrawal of the rejection of claims 57-60 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Bilodeau *et al.* (U.S. Patent Publication No. 2002/0137755).

VI. The Rejection of Claims 63-64 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 10 of the Office Action, the Examiner rejected claims 63-64 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Kovesdi *et al.* U.S. Patent Publication No. 2003/45498. Applicant respectfully disagrees.

The Examiner alleged that (1) D'Amato teaches the treatment of ocular neovascular diseases associated with angiogenesis (Column 1 line 65-66) including macular degeneration (column 2 line 3-6) with the analogues of instant compound in claim 49; and Kovesdi *et al.* teaches the several intervention methods including surgical intervention as part of the treatment.

Claims 63-64 depend on claim 49. As explained in section (IV) above, D'Amato does not teach or suggest the method of claim 49. Kovesdi *et al.* also does not teach or suggest the instant compound, much less the method of treating macular degeneration with the instant compound. Therefore, D'Amato and Kovesdi *et al.*, individually or in combination, do not teach or suggest the use of the method of claim 49 and thus claims 63-64 for treating macular degeneration as claimed.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 63-64 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Kovesdi *et al.* (U.S. Patent Publication No. 2003/45498).

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance.

A fee for one month extension is believed due for this submission. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: January 18, 2009

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